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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,855	10/18/2005	Eugene A. Woltering	ON/4-32726A	9609

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,855	WOLTERING, EUGENE A.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6-12 and 14-16* is/are pending in the application.

4a) Of the above claim(s) *15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2-4, 6-12 and 14-16 are presented for examination.

Applicant's Amendment filed February 19, 2010 has been received and entered into the present application.

Claims 2-4, 6-12 and 14-16 remain pending. Claims 15-16 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claims 2-4, 6-12 and 14 remain under examination. Claims 5 and 13 are cancelled. Claims 2, 4, 8, 10 and 12 are amended.

Applicant's arguments, filed February 19, 2010, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Error Noted in Claim Listing Dated February 19, 2010

Applicant has indicated the status of instant claims 15-16 as "Original" in the claim listing filed with the amendment submission dated February 19, 2010. However, as noted in the non-final rejection dated November 20, 2009, instant claims 15-16 are withdrawn from consideration as being directed to non-elected subject matter. Accordingly, claims 15-16 are withdrawn from examination, despite the incorrect status identifier provided in the claim listing of February 19, 2010.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-4 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter et al. (U.S. Patent Application Publication No. 2002/0119202; Issued August 29, 2002, Filed August 9, 2001) in view of Altmann et al. ("Epothilones and Related Structures-A New Class of Microtubule Inhibitors with Potent In Vivo Antitumor Activity", *Biochimica et Biophysica Acta*, 1470 (2000):M79-M91) and Cecil's Textbook of Medicine (Twenty-First Edition, Vol.2; 2000; p.1402-1403).

Hunter et al. teaches anti-angiogenic compositions, as well as methods for utilizing such compositions for the treatment of cancer and other angiogenesis-dependent diseases, wherein the composition comprises (a) an anti-angiogenic factor and (b) a polymeric carrier (p.2, para.[0014]). Hunter et al. teaches that the anti-angiogenic factor that may be used include, *inter alia*, anti-invasive factor, retinoic acid and derivatives thereof, paclitaxel, suramin, etc. (p.7, para.[0100]), and further discloses that, in preferred embodiments, the anti-angiogenic compositions may additionally comprise compounds in addition to the anti-angiogenic factor and polymeric carrier, such as, *inter alia*, one or more compounds that disrupt microtubule function, e.g., epothilone (p.9, para.[0114]). Hunter et al. teaches that the disclosed anti-angiogenic compositions may be employed in embolization therapy such that they are non-toxic, thrombogenic, easy to inject down vascular catheters, etc. (p.11, para.[0129]) for the treatment of benign tumors, including endocrine tumors, such as parathyroid adenomas (p.11, para.[0130]).

Note that, though Hunter et al. does not explicitly teach the treatment of recurrent or persistent parathyroid adenoma, the very teaching of "parathyroid adenoma" *per se* is understood to circumscribe both recurrent and persistent parathyroid adenoma, since recurrent or persistent adenoma provides for the two possible types of parathyroid adenoma that a subject suffering from said disease would exhibit (i.e., persistent, in the sense that it does not resolve, or recurrent, in that it resolves and returns). This genus of possible types of parathyroid adenoma is sufficiently limited in size so as to place each member of the genus within the possession of the public.

Hunter et al. fails to teach (1) the use of the particular epothilone compounds of the instant claims

(claims 2 and 4) or (2) that the hyperparathyroidism is primary hyperparathyroidism (claim 9).

Altmann et al. teaches epothilone compounds, such as those described in Fig.1 (i.e., epothilone A and epothilone B, which correspond to Applicant's instantly claimed epothilone structure of formula (I) wherein R is hydrogen for epothilone A or R is methyl for epothilone B; A is oxygen and R' is methyl; p.M80, col.1), that function as microtubule inhibitors with the ability to inhibit the growth of multi-drug resistant human cancer cell lines (p.M89, cols.1-2).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ any one of the epothilone compounds (e.g., epothilone A or B) in the anti-angiogenic composition disclosed by Hunter et al. as effective for the treatment of benign tumors, such as parathyroid adenoma, because Altmann et al. teaches that each of the disclosed epothilone compounds are one of a finite number of epothilone microtubule inhibitors known in the prior art at the time of the invention to predictably function as an anti-cancer agent. In other words, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ any one of the known anti-cancer epothilone microtubule inhibitors (which, as evidenced by Altmann et al., includes, *inter alia*, epothilone A or B) into the formulation of Hunter et al. for use in treating parathyroid adenoma with a reasonable expectation of success because (1) a person with ordinary skill in the art has good reason to pursue known options within his or her technical grasp (i.e., in the instant case, known anti-cancer epothilone microtubule inhibitor agents) and (2) Hunter et al. teaches the desirability of including such a microtubule inhibitor into the disclosed anti-angiogenic composition for the treatment of cancers, of which parathyroid adenoma is specifically named.

Cecil's Textbook of Medicine teaches that primary hyperparathyroidism is a disorder in which hypercalcemia is due to hypersecretion of parathyroid hormone and is caused by solitary adenomas in about 85% of cases (p.1402).

One of ordinary skill in the art at the time of the invention would have found it *prima facie*

obvious that the parathyroid adenomas to be treated by the method and compositions disclosed by Hunter et al. were the cause of primary hyperparathyroidism in the subject because, as evidenced by Cecil's, the majority of cases of primary hyperparathyroidism are caused by parathyroid adenomas. Such a person would have had a reasonable expectation of success in concluding this fact because it was well known in the art that parathyroid adenomas result in primary hyperparathyroidism, as opposed to other causes, such as renal failure (see Cecil's, p.1402,para.4), known to cause secondary hyperparathyroidism.

It is noted that Applicant defines the term "treating" as producing "one or more of the following effects in hyperparathyroidism patients", wherein the identified effects include a reduction in parathyroid hormone levels in blood, a reduction in parathyroid hormone levels in urine, a reduction of calcium levels in blood, a reduction of calcium levels in urine, and/or an increase in bone density. In view of the teachings of Hunter et al. in view of Altmann et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the anti-angiogenic composition of Hunter et al. in view of Altmann et al. for the treatment of parathyroid adenoma *per se* would have been reasonably expected to exert the same or substantially equivalent efficacy in reduction of parathyroid hormone levels and/or calcium levels resulting from parathyroid adenoma because: (1) Hunter et al. teaches that an anti-angiogenic composition that may further comprise an epothilone microtubule inhibitor was known to have efficacy in treating patients with benign tumors, such as parathyroid adenomas *per se* and (2) Cecil's teaches that the majority of cases of parathyroid adenomas result in primary hyperparathyroidism which causes hypercalcemia as a result of hypersecretion of parathyroid hormone. In other words, Hunter et al. in view of Altmann et al. provides the clear teaching that the disclosed anti-angiogenic composition comprising an epothilone microtubule inhibitor is, in fact, effective for treating all parathyroid adenoma patients, i.e., 100% of patients with parathyroid adenoma, without exclusion. Of this entire population of parathyroid adenoma patients, Cecil's provides the factual extrinsic evidence demonstrating that a subpopulation of such parathyroid adenoma patients also suffer from hyperparathyroidism that causes

hypercalcemia. Accordingly, the suggestion of Hunter et al. in view of Altmann et al. to use the disclosed formulation for treating any parathyroid adenoma patient is a clear suggestion to use it in any subpopulation of parathyroid adenoma patients, such as those suffering from concomitant hyperparathyroidism and hypercalcemia, with the reasonable expectation of the same (or at least substantially equivalent) level of efficacy in treating these subpopulations of patients via reducing levels of parathyroid hormone in blood or urine and/or calcium levels in blood or urine as would be expected in the treatment of parathyroid adenoma *per se*. Furthermore, since products of identical composition cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same host, whatever effect(s) the instantly claimed compound has in, e.g., reducing parathyroid hormone levels in blood or urine or reducing calcium levels in blood or urine, must necessarily be present in the method disclosed by Hunter et al. in view of Altmann et al. and further in view of Cecil's, absent factual evidence to the contrary.

In re Best (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation, the burden is shifted to the Applicants to "prove that the subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 592, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is, in fact, inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.,* 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). In the instant case, though the cited prior art may not expressly teach the effects of

reducing parathyroid hormone levels in the blood and/or urine, reducing calcium levels in the blood and/or urine or an increase in bone density, the cited prior art teaches the same active agent(s) as that presently claimed in the same amounts for administration to the same subject, and, therefore, these resultant effects on parathyroid or calcium levels and bone density must also be present, absent factual evidence to the contrary. The burden is now shifted to Applicant to prove that, in fact, the cited prior art does not possess these same claimed characteristics.

Claims 10-12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter et al. (U.S. Patent Application Publication No. 2002/0119202; Issued August 29, 2002, Filed August 9, 2001) in view of Altmann et al. ("Epothilones and Related Structures-A New Class of Microtubule Inhibitors with Potent In Vivo Antitumor Activity", *Biochimica et Biophysica Acta*, 1470 (2000):M79-M91) and further in view of Cecil's Textbook of Medicine (Twenty-First Edition, Vol.2; 2000; p.1402-1403).

Hunter et al. teaches anti-angiogenic compositions, as well as methods for utilizing such compositions for the treatment of cancer and other angiogenesis-dependent diseases, wherein the composition comprises (a) an anti-angiogenic factor and (b) a polymeric carrier (p.2, para.[0014]). Hunter et al. teaches that the anti-angiogenic factor that may be used include, *inter alia*, anti-invasive factor, retinoic acid and derivatives thereof, paclitaxel, suramin, etc. (p.7, para.[0100]), and further discloses that, in preferred embodiments, the anti-angiogenic compositions may additionally comprise compounds in addition to the anti-angiogenic factor and polymeric carrier, such as, *inter alia*, one or more compounds that disrupt microtubule function, e.g., epothilone (p.9, para.[0114]). Hunter et al. teaches that the disclosed anti-angiogenic compositions may be employed in embolization therapy such that they are non-toxic, thrombogenic, easy to inject down vascular catheters, etc. (p.11, para.[0129]) for the treatment of benign tumors, including endocrine tumors, such as parathyroid adenomas (p.11, para.[0130]).

Note that, though Hunter et al. does not explicitly teach the treatment of recurrent or persistent

parathyroid adenoma, the very teaching of "parathyroid adenoma" *per se* is understood to circumscribe both recurrent and persistent parathyroid adenoma, since recurrent or persistent adenoma provides for the two possible types of parathyroid adenoma that a subject suffering from said disease would have (i.e., persistent, in the sense that it does not resolve, or recurrent, in that it resolves and returns). This genus of possible types of parathyroid adenoma is sufficiently limited in size so as to place each member of the genus within the possession of the public.

Hunter et al. fails to teach (1) the use of the particular epothilone compounds of the instant claims (claims 10 and 12) or (2) the treatment of hypercalcemia resulting from parathyroid adenoma (claim 10).

Altmann et al. teaches epothilone compounds, such as those described in Fig.1 (i.e., epothilone A and epothilone B, which correspond to Applicant's instantly claimed epothilone structure of formula (I) wherein R is hydrogen for epothilone A or R is methyl for epothilone B; A is oxygen and R' is methyl; p.M80, col.1), that function as microtubule inhibitors with the ability to inhibit the growth of multi-drug resistant human cancer cell lines (p.M89, cols.1-2).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ any one of the epothilone compounds (e.g., epothilone A or B) in the anti-angiogenic composition disclosed by Hunter et al. as effective for the treatment of benign tumors, such as parathyroid adenoma, because Altmann et al. teaches that each of the disclosed epothilone compounds are one of a finite number of epothilone microtubule inhibitors known in the prior art at the time of the invention to predictably function as an anti-cancer agent. In other words, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ any one of the known anti-cancer epothilone microtubule inhibitors (which, as evidenced by Altmann et al., includes, *inter alia*, epothilone A or B) into the formulation of Hunter et al. for use in treating parathyroid adenoma with a reasonable expectation of success because (1) a person with ordinary skill in the art has good reason to pursue known options within his or her technical grasp (i.e., in the instant case, known anti-cancer epothilone

microtubule inhibitor agents) and (2) Hunter et al. teaches the desirability of including such a microtubule inhibitor into the disclosed anti-angiogenic composition for the treatment of cancers, of which parathyroid adenoma is specifically named.

Cecil's Textbook of Medicine teaches that primary hyperparathyroidism is a disorder in which hypercalcemia is due to hypersecretion of parathyroid hormone and is caused by solitary adenomas in about 85% of cases (p.1402).

In view of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the anti-angiogenic composition of Hunter et al. in view of Altmann et al. for the treatment of parathyroid adenoma *per se* would have been reasonably expected to exert the same or substantially equivalent efficacy in the treatment of hypercalcemia resulting from parathyroid adenoma because: (1) Hunter et al. teaches that an anti-angiogenic composition that may further comprise an epothilone microtubule inhibitor was known to have efficacy in treating patients with benign tumors, such as parathyroid adenomas *per se* and (2) Cecil's teaches that the majority of cases of parathyroid adenomas result in primary hyperparathyroidism which causes hypercalcemia. In other words, Hunter et al. in view of Altmann et al. provides the clear teaching that the disclosed anti-angiogenic composition comprising an epothilone microtubule inhibitor is, in fact, effective for treating all parathyroid adenoma patients, i.e., 100% of patients with parathyroid adenoma, without exclusion. Of this entire population of parathyroid adenoma patients, Cecil's provides the factual extrinsic evidence demonstrating that a subpopulation of such parathyroid adenoma patients also suffer from hyperparathyroidism that causes hypercalcemia as a result of hypersecretion of parathyroid hormone. Accordingly, the suggestion of Hunter et al. in view of Altmann et al. to use the disclosed formulation for treating any parathyroid adenoma patient is a clear suggestion to use it in any subpopulation of parathyroid adenoma patients, such as those suffering from concomitant hypercalcemia, with the reasonable expectation of the same (or at least substantially equivalent) level of efficacy in treating these subpopulations of patients as would be

expected in the treatment of parathyroid adenoma *per se*. Furthermore, since products of identical composition cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same host, whatever effect(s) the instantly claimed compound has in treating the concomitant hypercalcemia must necessarily be present in the method disclosed by Hunter et al. in view of Altmann et al. and further in view of Cecil's, absent factual evidence to the contrary.

In addition, it is noted that Applicant defines the term "treating" as producing "one or more of the following effects in hyperparathyroidism patients", wherein the identified effects include a reduction in parathyroid hormone levels in blood, a reduction in parathyroid hormone levels in urine, a reduction of calcium levels in blood, a reduction of calcium levels in urine, and/or an increase in bone density. *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation, the burden is shifted to the Applicants to "prove that the subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 592, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is, in fact, inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). In the instant case, though the cited prior art may not expressly teach the effects of reducing parathyroid hormone levels in the blood and/or urine, reducing calcium levels in the blood and/or urine or an increase in bone density, the cited prior art teaches the same active agent(s) as that presently claimed in the same amounts for administration to the same subject, and, therefore, these resultant effects on parathyroid

hormone or calcium levels and bone density must also be present, absent factual evidence to the contrary. The burden is now shifted to Applicant to prove that, in fact, the cited prior art does not possess these same claimed characteristics.

Conclusion

Rejection of claims 2-4, 6-12 and 14 is proper.

Claims 15-16 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Primary Examiner, Art Unit 1614

May 17, 2010